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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,294	02/17/2004	Steven W. Dow	JUVARIS1110	8023

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
12/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,294	DOW ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of August 20, 2009, to the non-final action dated March 20, 2009, has been entered. Claims 1 and 13 have been amended. No claims were cancelled or newly added. Claims 1-10 and 13-22 are pending in the application and are currently under examination. The claims have been examined commensurate in scope with the elected species of an oligonucleotide containing no CpG motifs.

Withdrawn Claim Rejections - 35 USC § 112 – Written Description

Claims 1-10 and 13-22 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, in the previous office action dated March 20, 2009. Applicants have amended base claims 1 and 13 to replace "DNA molecule" with "oligodeoxynucleotide", obviating the ground or rejection. Accordingly, the rejection is hereby withdrawn.

Withdrawn Claim Rejections - 35 USC § 112 - Scope of Enablement

Claims 1-10 and 13-22 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicants' have amended the claims commensurate with the enabled scope previously indicated, and further deleted "therapeutic" from the claims, thereby obviating the grounds for rejection. Thus, the rejection is hereby withdrawn.

Response & Maintained Claim Rejections - 35 USC § 103

Claims 1-7, 10, 13-19, and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Auf et al. (Clin. Cancer Res. 7:3540-3543; 2001), in view of Vollmer et al. (Antisense & Nucl. Acid Drug Dev. 12:165-175; 2002), and further in view of Tam et al. (U.S. Patent Publication No.: 2004/0009944; effective filing date May 10, 2002). The rejection set

forth on pp. 6-9 of the previous Office action dated March 20, 2009 is maintained for reasons of record.

The Rejection:

The claims embrace a composition comprising a liposome delivery vehicle and an oligodeoxynucleotide from more than 25 to about 100 nucleotides in length containing no CpG motifs, having the ability to elicit a systemic non-antigen specific Th1 immune response in a mammal, and a method comprising administering said composition to a mammal.

It is noted that base claim 1 is directed to a composition comprising a liposome delivery vehicle and an oligodeoxynucleotide. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Auf et al. describe phosphorothioate oligodeoxynucleotides containing CpG motifs that display immunostimulating activity without antigen, in rats and mice, inducing tumor rejections through an early activation of innate immunity and priming of a specific immune response against glioma cells (Title and Abstract). Auf et al. further describe a 22mer oligodeoxynucleotide in which the CpG motifs have been mutated (second column, p. 3540), that when administered to rats, resulted in a lesser reduction in tumor volume than a corresponding oligodeoxynucleotide containing two CpG motifs (Fig. 1, p. 3541).

While the oligodeoxynucleotide described by Auf et al. having no CpG motifs was not greater than 25 nucleotides in length, and was not administered with a liposome delivery vehicle, such were known in the prior art.

Vollmer et al. describe highly immunostimulatory CpG-free oligodeoxynucleotides for activation of human leukocytes, having length-dependent immunostimulatory effects, and less efficient in stimulating human immune cells (Title and Abstract). Vollmer et al. specifically describe CpG-free oligodeoxynucleotides having 27 and 30 nucleotides in length, in Table 1, p. 166, thus curing the deficiency in Auf et al. for oligodeoxynucleotide length.

Tam et al. describe immunostimulatory oligonucleotides bearing methylated CpG dinucleotide motifs encapsulated in a lipid particle for *in vivo* use (Title and Abstract). The lipid particle is further described as a liposomal particle comprising a cationic lipid selected from a group of cationic lipids consisting of DDAB, DODAC, DOTAP, DMRIE, DOSPA, DMDMA, DC-Chol, DODMA DODAP (paragraph [0016], and DOTMA (paragraph [0098], and wherein the lipid particle preferably comprises cholesterol (paragraphs [0406] and [0119]). Extruded lipids are described in paragraph [0123], and the liposomes are further disclosed as preferably multilamellar (paragraph [0078]). The lipid-nucleic acid formulation further comprises a pharmaceutically acceptable carrier, buffer or diluent (paragraph [0014]). With regard to the nucleic acid to lipid ratios, Tam et al. state that dosages of lipid-nucleic acid formulations depend on the desired drug:lipid ratio of the composition, and one skilled in the art can select proper dosages based on the information provided (paragraph [0172]). Applicants should further note that as indicated in MPEP 2144.05: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Routine optimization is not inventive, and no evidence has been presented here to suggest that the selection of the claimed nucleic acid to lipid rations was other than routine or that the results should be considered unexpected. The non-criticality of the concentration ratio is evidenced by the wide range claimed.

The compositions and methods described by Auf et al., Vollmer et al. and Tam et al. are directed to the delivery of oligodeoxynucleotides to elicit an immune response. Thus a person of ordinary skill in the art would have been motivated to combine their respective teachings to elicit a systemic non-antigen specific immune response in a mammal.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of non-CpG containing oligodeoxynucleotides and liposome delivery particles, resulting in the composition and method of the instantly claimed invention, with a reasonable expectation of success. It should be noted

that the ability of the composition to elicit a Th1 immune response in a mammal is a property inherent to the composition.

As stated in MPEP 2112: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Moreover, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim. See, e.g., *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed.Cir. 1997).

Response to Arguments:

Applicants traverse the rejection, arguing that Auf teaches away from a composition comprising a liposome delivery vehicle and an oligodeoxynucleotide from more than about 25 to about 100 nucleotides in length containing no CpG motifs, having the ability to elicit a systemic non-antigen specific Thl immune response in a mammal; that in Figure 1, the authors state the IMM-ODNs did not lead to significant tumor reduction, and in the discussion Auf states that "CpG motifs within the ODN were critical to trigger the immune response, for an ODN without such motifs was inefficient." Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that instant claims 1-10 are directed to a composition, and such composition is specifically taught by the cited references. As stated in MPEP 2112: "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman*

Instruments v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).

With respect to Figure 1 of Auf et al., the Figure while showing that non-CpG-ODN had a lesser effect on reducing tumor volume that CpG-ODN, cannot be considered a teaching away, because the instant method claims only require that non-CpG oligos be administered and elicit a Th1 immune response. Significant tumor volume reduction as compared to CpG-ODNs is not a requirement in the instantly claimed method. The fact that ODN without a CpG-motif is inefficient (as recited by Auf et al., under discussion), does not indicate that such ODN cannot elicit a Th1 response. Moreover, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that although Vollmer comprises immunostimulatory CpG-free oligodeoxynucleotides, it comprises the use of methylated CpG ODNs to stimulate a Th2 immune response.

Such is not found persuasive, because Vollmer et al. describe both non-CpG ODNs rich in thymidine as well as ODNs with methylated CpG motifs, having length-dependent immunostimulatory effects (Abstract).

Applicants argue that Vollmer teaches away from using non-methylated CpG ODNs by stating "the 20-mer thymidine homopolyrner used for these studies gave a Th2-1ike antibody response on immunization, in contrast to Thl-like responses with CpG ODNs." And that "in vitro longer non- CpG thymidine rich ODNs are always less efficient and potent than CpG ODNs, and, therefore, they might induce weaker *in vivo* effects that are not sufficient to mediate efficiently a Thl- dominated immune response."

In response, it should be noted that Applicants' reading of Vollmer et al. is clearly selective, because Vollmer et al. additionally state that it can be speculated that short non-CpG PS-ODN induces only minimal stimulation *in vivo* as well as *in vitro*, and that longer ODNS (≥24 nt) are needed to induce stronger stimulation. Further stating: "In addition, the mechanism of immune activation by non-CpG ODNs remains to be elucidated" (second column, p. 173).

Thus, Vollmer et al. clearly suggest that longer non-CpG ODNs (≥24 nt) may be sufficient to induce a Th1 mediated immune response.

Applicants argue that the references all teach different kinds of ODNs or entirely different targets, and/or mechanisms and results, and thus a person of ordinary skill in the art would not have been motivated to combine their respective teachings.

Such is not found persuasive, because all three references teach immunostimulatory oligonucleotides, and the use of oligonucleotides in a lipid particle was known in the prior art. Thus, it would have been *prima facie* obvious to someone of ordinary skill in the art to utilize the oligodeoxynucleotides of Auf or Vollmer in a liposome delivery particle.

Thus, the rejection is maintained for reasons of record and the foregoing commentary.

Claims 1, 7-9, 13 and 19-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Auf et al. (Clin. Cancer Res. 7:3540-3543; 2001), in view of Vollmer et al. (Antisense & Nucl. Acid Drug Dev. 12:165-175; 2002), and Tam et al. (U.S. Patent Publication No.: 2004/0009944; effective filing date May 10, 2002), as applied to claims 1-7, 10, 13-19, and 22 above, and further in view of Klinman et al. (U.S. Patent Publication No.: 2003/0060440; filed Feb. 6, 2002).

The Rejection:

The claims encompass a composition comprising a liposome delivery vehicle and an oligodeoxynucleotide from more than 25 to about 100 nucleotides in length containing no CpG motifs, comprising dextrose in water as an excipient, having the ability to elicit a systemic non-antigen specific Th1 immune response in a mammal, and a method comprising administering said composition to a mammal. The specification exemplifies dextrose in water as a non-ionic diluent.

Auf et al. describe phosphorothioate oligodeoxynucleotides containing CpG motifs that display immunostimulating activity without antigen, in rats and mice, inducing tumor rejections through an early activation of innate immunity and priming of a specific immune response against glioma cells (Title and Abstract). Auf et al. further describe a 22mer

oligodeoxynucleotide in which the CpG motifs have been mutated (second column, p. 3540), that when administered to rats, resulted in a lesser reduction in tumor volume than a corresponding oligodeoxynucleotide containing two CpG motifs (Fig. 1, p. 3541).

Vollmer et al. describe highly immunostimulatory CpG-free oligodeoxynucleotides having 27 and 30 nucleotides in length, in Table 1, p. 166.

Tam et al. describe immunostimulatory oligonucleotides bearing methylated CpG dinucleotide motifs encapsulated in a lipid particle for *in vivo* use (Title and Abstract). The lipid-nucleic acid formulation further comprises a pharmaceutically acceptable carrier, buffer or diluent (paragraph [0014]).

While the pharmaceutical diluent composition described by Tam et al. did not comprise dextrose, such were known in the prior art.

Klinman et al. describe oligodeoxynucleotides comprising a CpG motif for inducing an immune response (Abstract), formulated in a pharmaceutically acceptable fluid such as water, that include aqueous dextrose (paragraph [0092]). As indicated above, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

The compositions and methods described by Tam et al. and Klinman et al. are directed to the delivery of oligodeoxynucleotides to elicit an immune response. Thus a person of ordinary skill in the art would have been motivated to combine their respective teachings to elicit a systemic non-antigen specific immune response in a mammal.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize aqueous dextrose in a pharmaceutical formation of oligodeoxynucleotides and liposome delivery particles, resulting in the composition and method of the instantly claimed invention, with a reasonable expectation of success.

Response to Arguments:

Applicants traverse the rejection, arguing the cited references do not teach all of the claimed elements, and that there is no motivation to modify the methods. Applicants' arguments

have been fully considered, but are not found persuasive. Applicants are directed to the response set forth above.

Thus, the rejection is maintained for reasons of record and the preceding discussion.

Citation of Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicants' disclosure. Bratzler et al. describe immunostimulatory nucleic acids that may be administered to subjects (Abstract). The nucleic acids are preferably in the range of 6 to 100 bases in length (paragraph [0047). A non-CpG immunostimulatory nucleic acid is a nucleic acid which does not have a CpG motif in its sequence, regardless of whether the C is the dinucleotide is methylated or unmethylated. Non-CpG immunostimulatory nucleic acids may induce Th1 or Th2 immune responses, depending upon their sequence, their mode of delivery and the dose at which they are administered (paragraph [0049]). Additionally disclosed are liposomes as delivery vectors (paragraph [0146]), Including DOTMA (paragraph [0149], as well as cholesterol (paragraph [0167]).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633